obvious over the '015 application in combination with the teaching of Hilberg, Holland, Franz, and Weiher. Given that the Applicants have abandoned the '015 application, the above obviousness rejections that are based on the '015 application are also deemed to be moot.

B. Prior art rejections based on 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 7, 8, 20 and 21 as anticipated by Temin under 35 U.S.C. § 102(b).

Anticipation is established only when a single unit of prior art discloses, expressly or under inherency principles, each and every element of the claimed invention. In re Bond, 910 F.2d 831, 832 (Fed. Cir. 1990).

As amended, the present claims require that the retroviral vectors not contain a gene encoding a complete (i.e., functional) selectable marker. A careful review of Temin shows that it fails to teach recombinant retroviral vectors that do not contain genes encoding selectable markers. Since Temin does not teach vectors with each and every element of the present claims, the Examiner's rejection under § 102(b) is improper and should be withdrawn.

C. Prior art rejections under 35 U.S.C. § 103.

Where the prior art, as a whole, does not explicitly suggest the claimed process, a proper obviousness analysis under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process; and (2) whether the prior art would have also revealed that in so carrying out, those of ordinary skill would have a reasonable expectation of success, In re Vaeck, 947 F.2d 488, 493

(Fed.Cir.1991). A key facet of the above quote is that the cited prior art must provide teaching sufficient to give one of ordinary skill a reasonable expectation of success. In other words, if the Examiner fails to establish that there would have been a reasonable expectation of success, the Examiner has also failed to present a bona fide *prima facie* case of obviousness.

The Examiner's rejection of claims 2-4 and 20 as unpatentable under 35 U.S.C. § 103 over the combined teaching of Temin and Bender *et al*. (Bender) is respectfully traversed. Neither Temin nor Bender teach or suggest recombinant retroviral vectors that are capable of transducing mammalian cells without selection. Accordingly, Temin and Bender cannot be combined to teach recombinant retroviral vectors which lack a complete selectable marker. Given that neither Temin nor Bender teach or suggest at least one element of the present claims, the Examiner's rejection is no longer appropriate and should be withdrawn.

Claims 5, 6, and 20 have also been rejected under 35 U.S.C. § 103 as obvious over the combined teachings of Temin, Bender, and Cone and Mulligan (Cone). The language from claim 5 has been merged into claim 1, and claim 5 has subsequently been canceled. Thus, the rejection of claim 5 is no longer at issue.

As discussed above, Temin and Bender are largely irrelevant to the present claims. Cone merely provides a conclusory comment that titers approaching 10^5 per ml might enable the nonselective introduction of genes into 100% of a population of cells. However, Cone describes no experiments,

and provides no data to support the comment. Given the lack of specific guidance, it is clear that Cone's wholly unsupported commentary merely provides an invitation for further experimentation.

Moreover, the Examiner is respectfully reminded that, like Temin and Bender, Cone does not teach or suggest the construction of retroviral vectors that lack a complete selectable marker. Accordingly, the Examiner may not credibly argue that Cone provides teaching that would have provided one of ordinary skill with the requisite expectation of successfully producing the claimed vectors.

In fact, subsequent studies by Cone's coauthor (one of the present Applicants) revealed that Cone's suggested titer is nearly an order of magnitude lower than the titers actually needed to achieve the practical nonselective introduction of genes into mammalian cells[2]. Thus, even applying hindsight, it is clear that one of ordinary skill could not have combined the vectors and packaging cell lines taught by cited references to practice the presently claimed invention. The Applicants respectfully submit that it is axiomatic that an inoperative combination can not provide one of ordinary skill with teaching sufficient to provide a reasonable expectation of success. In view of this fact, the Applicants submit that the cited references do not support a *prima facie* case of obviousness under § 103, and the Examiner is respectfully requested to withdraw the rejections of claims 6 and 20.

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[2]Like Pauling and Corey's infamous DNA triple helix, Cone's premature disclosure simply turns out to be wrong.

The Examiner has rejected claims 9 and 20 under § 103 as obvious over Temin, taken in view of Kenten *et al*. (Kenten), or Kuo *et al*. (Kuo). As amended, claims 9 and 20 are respectively directed to a particular class of novel retroviral vectors (that do not encode a complete selectable marker) which encode either tPA or factor VIII, and cell lines transfected with the same. Again, the Applicants submit that none of Temin, Kuo, and Kenten suggest retroviral vectors which do not encode a complete selectable marker. Thus, the Applicants respectfully request that the Examiner withdraw the rejection of claim 9.

Similarly, none of Temin, Kuo, or Kenten suggest the construction of cell lines without a selection step. Since claim 20 only reads on cell lines that have been transfected with the novel class of retroviral vectors described in the present invention (the use of which proscribes a selection step), the Examiner's rejection of claim 20 is no longer germane, and should be withdrawn.

The Examiner has also rejected claims 10, 11, 17, 18 and 20 under § 103 as obvious over the combined teaching of Temin and Emerman *et al*. (Emerman). The present claims have been amended to recite that the claimed retroviral vectors do not encode a complete selectable marker. Neither Emerman nor Temin teach or suggest such vectors, therefore, the rejection of claims 10, 11, 17, 18, and 20 is not appropriate and should be withdrawn.

The Examiner has rejected claims 16 and 20 under § 103 as obvious over Temin, Emerman, Yee *et al*. (Yee), and Yu *et al*. (Yu). Temin and Emerman are discussed, *supra*. Neither Yee

nor Yu teach retroviral vectors which do not encode complete selectable markers. Moreover, none of the cited references provide a suggestion or motivation for constructing vectors comprising the presently claimed elements. As such, the Applicants respectfully submit that the Examiner's rejection of claims 16 and 20 should be withdrawn.

The Examiner has also rejected claim 19 under § 103 as obvious over Temin, Emerman, Kenten, and Kuo. While it may have been obvious to use the prior art retroviral vectors to express factor VIII or tPA, the cited references provide no suggestion or motivation for expressing tPA or factor VIII using the vectors comprising the presently claimed elements. Accordingly, the Examiner is respectfully requested to withdraw the rejection of claim 19.

Claims 12-15, 20 and 22 have been rejected as unpatentable over Temin, Emerman, in view of Anderson and deVilliers. Again, the Applicants respectfully direct the Examiner's attention to the fact that none of the cited references teach or suggest retroviral vectors which do not encode a complete selectable marker. Since the absence of a selectable marker is an element of the present claims, the Examiner's rejection of claims 12-15, 20 and 22 is no longer appropriate and should be withdrawn.

The Examiner has also rejected claim 22 under 35 U.S.C. § 103 as obvious over Temin, in view of Anderson or deVilliers. For the reasons discussed immediately above, and given the present claims amendments, the Applicants respectfully submit that the Examiner's rejection claim 22 should be withdrawn.

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The Examiner has also rejected claims 23 and 24 under 35 U.S.C. § 103 as unpatentable over Temin, Anderson, deVilliers, in further view of Hilberg or Holland. While the cited references provide an impressive array of regulatory features, the cited references, as a whole, do not teach or suggest retroviral vectors that do not encode a complete selectable marker. Accordingly, the Examiner is respectfully requested to withdraw the rejection of claims 23 and 24.

Claims 25-31 have been rejected under § 103 as obvious over the combined teaching of Temin, Anderson, deVilliers, in further view of Hilberg, or Holland, and in further view of either Franz or Weiher. Again, the references cited by the Examiner embody a fairly comprehensive overview of the state of the prior art developments in retroviral vector design and use. However, the Examiner has not shown where or how the cited references, as a whole, teach or suggest the salient features of the novel vectors claimed in the present application. In fact, the cited art fails to even recognize that problem that the present invention was designed to circumvent; i.e., the need for novel vectors that efficiently transduce cells without requiring a selection step.

The Examiner is respectfully requested to consider that case law clearly holds that non-obviousness can lie in the discovery of a problem, the solution to which employs the combination of old elements, see, In re Sponnoble, 160 USPQ 237 (CCPA 1969). Moreover, the non-obviousness involved in the discovery of the reason for the problem can impart patentability to the solution thereto, even though by hind-sight the cause of the problem once recognized may suggest the

solution. In re Leonnart and Espy, 135 USPQ 307 (CCPA 1962), Trio Process Corp. v. L. Goldsteins Sons, Inc., 174 USPQ 129 (CA3 1972), In re Roberts et al., 176 USPQ 313 (CCPA 1973), In re Nomiya et al., 184 USPQ 607 (CCPA 1975), Ex parte Campbell et al., 211 USPQ 575 (POBA 1980). Additionally, the Examiner is directed to In re Peehs and Hunner 204 USPQ 835 (CCPA 1980), where the Court stated:

> Where the Applicant contends that the discovery of the source of a problem would have been unobvious [non-obvious] to one of ordinary skill in the pertinent art at the time the claimed invention was made, it is incumbent upon the PTO to explain its reasons if it disagrees. A mere conclusionary statement that the source of a problem would have been discovered is inadequate. As this court explained in In re Sponnoble, 56 CCPA 823, 832, 405 F.2d 578, 585, 160 USPQ 237, 243 (1969): "A patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103."

Simply put, none of the publications cited by the Examiner, alone or in combination, suggest that it may be desirable to construct retroviral vectors which do not encode complete selectable markers. Thus, it is axiomatic that since none of the cited references even recognized the problem, the references, alone or in combination, could not have motivated or suggested the solution to one of ordinary skill in the art. Absent such motivation or suggestion, the cited art cannot properly support a *prima facie* case of obviousness under 35 U.S.C. § 103.

Given the above perspective, the Applicants respectfully submit that the presently claimed vectors (which do not encode a complete selectable marker) are *per se* nonobvious, and,

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accordingly, the Examiner is respectfully requested to withdraw the rejections of claims 2-6, 9-20, and 22-31 under 35 U.S.C. § 103.

III. Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1-31 because of certain objections to the specification for failing to provide an adequate written description of the invention. In particular, the Examiner has cited the specification at page 10, lines 27-28 where a typographical error resulted in several unlabeled boxes which correspond to regions of Fig. 10. The Examiner has also objected to specification because of the uncertainty regarding certain descriptions of the "αG-SGC" vector (a typographical error that should have simply recited "α-SGC"), and the nature of the "improvements" inherent in α-SGC-LacZ.

The Applicants have amended the specification to correct the typographical errors to which the Examiner has objected. Given the detailed description of α-SGC in Fig. 4, the typographical corrections to page 10 of the specification are not deemed to constitute new matter. The Applicants propose that the typographical error present in Fig. 11 will be corrected at the time formal drawings are submitted.

Regarding the confusion over α-SGC/αG-SGC, the Applicants have amended the specification to correct the typographical error that caused the confusion over "αG-SGC".

Regarding α-SGC-LacZ, the vector is "improved" in that it provides a simple and well-established assay for studying retroviral transduction and gene expression both *in vitro* and *in vivo*. In addition to the above capability, the vector may

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still be used to transduce cells with a gene of interest that has been inserted into the vector.

Claims 1-6, 8-11, 15, 17-21, and 24 have been rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Applicants have amended claim 1 and 21 to address the Examiner's comments by deleting the phrase "operable combination", and more particularly detailing the arrangement of the various elements. In view of these amendments, the Examiner is respectfully requested to withdraw the rejection of claims 1 and 21 under § 112, second paragraph.

Regarding claim 2, the Applicants submit that one of ordinary skill would clearly understand that the term "a portion of *gag* sequence" represents any *gag* sequence that is other that a complete *gag* gene. Moreover, the Applicants have amended to claim 2 to recite where the portion of *gag* sequence is located in the vector. In view of this amendment and these remarks, the Examiner is respectfully requested to withdraw the rejection of claim 2 under § 112, second paragraph.

Claim 3 has been amended to address the Examiner's comments, and thus the rejection under § 112 has been avoided by amendment.

Regarding claim 4, the Applicants' submit that one of ordinary skill would understand that the term "*gag* transcriptional promoter" refers to any promoter that directs the transcription of the portion of *gag* sequence described in claim 3. Accordingly, the Applicants have amended the claim by deleting the word "*gag*" in order to remove any ambiguity as

to the nature of the promoter. In view of the above explanation, and the amendment of claims 3 and 4, the Examiner is respectfully requested to withdraw the rejection of claim 4 under 35 U.S.C. § 112, second paragraph.

The Applicants have canceled claim 5, and merged the claim into amended claim 1. Accordingly, the Examiner's rejection under 35 U.S.C. § 112, second paragraph has been rendered moot.

Claims 6 and 15 have been amended as requested by the Examiner, and thus the Examiner's rejection of claims 6 and 15 are no longer appropriate and should be withdrawn.

Claims 8 and 18 have also been amended to delete the word "drug" and thus the Examiner's rejection under 35 U.S.C. § 112, second paragraph has been avoided by amendment.

Claims 9 and 19 have also been amended to avoid the Examiner's rejection under 35 U.S.C. § 112, second paragraph.

Claim 10 has been amended to more particularly recite where the α-globin promoter is positioned in the vector. Thus, the Examiner's rejection of claim 10 is deemed to have been avoided by amendment.

Regarding claim 11, the Applicants have avoided the Examiner's rejection by amending the claim to use consistent designations for the word "alpha".

The Applicants have amended claim 10 (upon which claim 17 is dependent), and the amendment is deemed to have substantially avoided the Examiner's rejection. In addition, the Applicants respectfully submit that one of ordinary skill would understand that either or both of the 5' LTR or alpha-globin promoters may direct the transcription of a gene which

has been placed, in the obvious and proper orientation[3], into the insertion site of the vector. One of ordinary skill would also understand that differential expression may occur from the two promoters depending on the tissue/cellular environment in which the vector had been transduced.

Claims 20 and 24 have been amended to correct the respective form and spelling of the claims.

No substantive "nonenablement" rejections are presently pending. This position is clearly proper since the Applicants' have disclosed in the specification at least six operative species of vector/insert combinations that are each exemplary of the generically claimed genus (retroviral vectors which enable transduction without selection).

The Applicants' Attorney is presently attempting to cure the defective Oaths and Declarations of Drs. Rafield and Robbins. Corrected versions will be expeditiously forwarded to the Examiner after receipt by the Attorney of record.

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe that the application is in good and proper condition for allowance. Early notification to that effect is earnestly solicited. If the Examiner feels that a telephone call would expedite the consideration of the application, the

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[3]The Examiner is also requested to consider that the presently claimed vectors may be used in anti-sense studies where the orientation of the gene of interest will be reversed, and the desired "expression" is not necessarily directed to a producing protein.

Examiner is invited to call the undersigned attorney at (415) 926-7405.

Respectfully submitted,

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